Ventilator-Associated Pneumonia

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March 17th, 2004

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Introduction

Ventilator-Associated pneumonia (VAP) is generally defined as a nosocomial pneumonia which develops in patients who have received mechanical ventilation (MV), either by endotracheal intubation or tracheostomy, for greater than 48 hours. It can be divided into early-onset versus late-onset VAP. Early-onset VAP occurs within the first 3-4 days of MV and is typically due to community acquired organisms such *Streptococcus pneumoniae*, *Hemophilus influenza*, and Methacillin-Sensitive *Staphylococcus aureus*. While late-onset VAP develops after 4 days of MV, it is commonly caused by a polymicrobial infection with virulent and often resistant pathogens such as *Pseudomonas aeruginosa*, *Acinetobacter baumanii*, and Methacillin-Resistant *Staphylococcus aureus*. Ventilator-associated pneumonia is the second most common infection acquired in the intensive care unit (ICU); it is the first in Europe (1, 2). It is felt to be responsible for up to half of all antibiotics used in the ICU. It represents 80% of all hospital acquired pneumonias (3). VAP is associated with a significant morbidity and mortality, with mortality rates as high as 80% reported. Although there is much information about VAP in the literature, the data are difficult to interpret due to a lack of standardized criteria for diagnosis.

Epidemiology

The risk of pneumonia in intubated patients is 10-21 times greater than in patients who are not intubated (4, 5). The cumulative risk for development of VAP increases overtime at a rate of approximately 1% per day (6). This risk is concentrated in the first 5-10 days of mechanical ventilation, with the daily hazard rate at day 5 of 3%, at day 10 of 2% and at day 15 of 1% (7).

The incidence of VAP varies from 5-65% (8). The large variability reported likely represents different diagnostic techniques used as well as different patient populations studied. Surgical patients are at increased risk for development of VAP when compared to medical patients. A study by Kollef found the highest incidence in CT ICU patients at 21.6%; then SICU patients at 14%; and MICU patients at 9.3% (9). A multivariate analysis by Cook et al identified the following independent predictors for the development of VAP: burns (RR, 5.09 [95% CI 1.52 to 17.03]), trauma (RR 5.00 [CI 1.91 to 13.11]), central nervous system disease (RR 3.40 [CI 1.31 to 8.81]), respiratory disease (RR 2.79 [CI 1.04 to 7.51]), cardiac disease (RR 2.72 [CI 1.05 to 7.01]), MV in the previous 24 hours (RR 2.28 [CI 1.11 to 4.68]), witnessed aspiration (RR 3.25 [CI 1.62 to 6.50]), and paralytic agents (RR 1.57 [CI 1.03 to 2.39]) (7).

Crude mortality rates of 24-76% have been reported for patients with VAP (8). There is controversy, however, about whether this increase in mortality is attributed to VAP versus underlying illnesses. Seven studies using matched case-controls have been done to evaluate the attributable mortality. Four of these studies found a mortality of 15-50%, while 3 studies failed to find any significant mortality associated with VAP (8). Many researches feel that patients with VAP are sicker than patients without VAP and therefore are more likely to die from their underlying disease processes. Certain subgroups, however, do have an increased mortality associated with VAP. These subgroups include: those with late onset VAP (more virulent, multi-resistant pathogens), those whose initial antibiotic regimen was later deemed to be inappropriate and medical patients when compared with surgical patients (10, 11, 12, 13, 14, 15).

The development of VAP leads to an increased length of stay in the ICU. One study found patients with VAP stayed in the ICU an average of 4.3 days longer than patients without VAP (15). Rello et al, in the largest epidemiologic study in the US to date, did a retrospective cohort to look at outcomes in VAP (16). They found that patients with VAP spent an extra 6.1 days in the ICU, an extra 11.5 days on MV, and an extra 10.6 days in the hospital. In this same study the cost of VAP was found to be > $40,000 in mean hospital charges.

Pathogenesis

Bacteria which reach the lower respiratory tract and overwhelm local defenses are responsible for the development of VAP. These bacteria may reach the lungs via 4 mechanisms: aspiration, inhalation, hematogenous spread and translocation. Translocation, or the movement of bacteria from the lumen of the GI tract through the epithelial mucosa to the mesenteric lymph nodes and finally to the lung, has been described in animal models but there is insufficient evidence at this time to ascribe to human beings. Hematogenous spread may occur, but is extremely rare. Translocation and hematogenous spread will not be discussed further.

Inhalation of aerosols containing bacteria is usually the result of contaminated respiratory therapy equipment. This may be due to cross contamination (such as inadequate hand washing or inappropriate use of gloves), inadequate disinfection and sterilization techniques or contamination of inhaled solutions.

Micro-aspiration is thought to be the most important mechanism in development of VAP. Bacterial colonization of the oropharynx and the upper air way followed by aspiration may lead to VAP if the bacterial burden is significant, the pathogen is particularly virulent or the host defenses are impaired. Bacterial colonization is common place in the ICU. A study by Johanson et al found that 45% of patients in the ICU were colonized with gram-negative bacilli (GNB) within one week of admission (17). In addition many of these patients are at increased risk of aspiration due to the following: depressed level of consciousness (due to underlying disease, sedation or paralytic agents), dysphagia (secondary to neurologic or esophageal disorders), the use of endotracheal tubes and enteral tubes (both nasogastric and orogastric), enteral nutrition and lying in the supine position.

Risk Factors

The most important risk factor for development of VAP is intubation. Aside from intubation, many independent factors have been isolated and these are summarized in table 1. Interestingly, antibiotic exposure has been found to be both protective against VAP and a risk factor for its' development, depending on the time given (9, 18). The prior use of antibiotics has been found to be protective against VAP in a subset of patients, typically those patients who receive antibiotics within 48 hours of the development of early-onset VAP. Other studies, however, have found prior antibiotic exposure to be a significant risk factor for VAP and the development of multi-resistant pathogens. A prospective study by Trouillet et al done to evaluate risk factors for the development of VAP due to potentially drug resistant bacteria looked at 135 episodes of VAP over 25 months. Using logistic regression analysis 3 factors were found to be significant: duration of mechanical ventilation for > 7 days (OR 6.0), prior antibiotic use (OR 13.5) and prior use of broad spectrum antibiotics (OR 4.1) (19).

Table 1. Independent Risk Factors for the development of Ventilator-Associated Pneumonia

Host Factors	Interventional Factors
Serum Albumin < 2.2 g/dl	Re-intubation
Age > 60 years	MV > 2 days
ARDS	Frequent ventilator circuit changes
COPD, pulmonary disease	Paralytic agents, sedation
Coma or impaired consciousness	Nasogastric tube
Burns	Maintenance of supine head position
Trauma	H2 blockers, antacids
Organ failure	Transport out of ICU for tests
Severity of illness	Prior antibiotic use
Large volume gastric aspiration	Prior use of broad spectrum antibiotics
Gastric colonization and pH	
Upper respiratory tract colonization	
Sinusitis	

This table was modified from Chastre et al (8)

Prevention

Airway and secretion management

The transmission of virulent pathogens from one patient to another via the contaminated hands of healthcare workers is a significant concern. Hand washing and the use of gloves (that are changes in between each patient) are effective in removing transient bacteria and preventing this transmission (20). The routine use of protective gown and gloves, however, is effective only when directed at specific antibiotic resistant pathogens (21).

Prolonged nasotracheal intubation has been associated with increase risk of sinusitis. Since sinusitis may lead to VAP via aspiration of infected secretions, nasotracheal intubation has been implicated as a possible risk factor for VAP. A randomized, controlled trial by Holzapfel et al looked at the influence of the route of intubation on both sinusitis and pneumonia and showed a trend toward increased pneumonia in patients who were nasally intubated (22).

Secretions pool above the cuff of the endotracheal tube and may be aspirated leading to development of VAP. Endotracheal tubes are available with a suction port above the cuff through which secretions may be removed. Several studies have shown a decrease in VAP associated with continuous subglottic secretion drainage (23, 24). Routine drainage of subglottic secretions is only effective if adequate cuff pressure is maintained to prevent leakage around the cuff. The cuff pressure should be maintained between 25 and 30 cm of water, higher pressures should be avoided to prevent tracheal injury (25).

The presence of an artificial airway alone is the single most important risk factor for the development of VAP. The endotracheal tube acts to hold the vocal cords open, which facilitates aspiration; impairs local host defenses; and creates a biofilm which is a reservoir for bacteria, all leading to an increased risk of VAP. The duration of MV is also associated with increased rate of development of VAP. The use of non-invasive positive pressure ventilation (NPPV) as an alternative to intubation or an adjunct to weaning has been considered to prevent VAP. Several studies have reported a decrease in VAP using NPPV versus mechanical ventilation and intubation (26, 27, 28).

Patients who require re-intubation are at increased risk for the development of VAP (29). This is thought to be due to an increase in micro-aspirations or large volume gastric aspiration at the time of re-intubation. Avoidance of unnecessary extubation with the use of chemical and physical restraints may be warranted.

Maintenance of the supine position leads to retention of airway secretions with subsequent aspiration, which may in turn lead to the development of VAP. With this information, the placement of patients in the semi recumbent position and the use of kinetic or oscillating beds have been studied to prevent VAP. A study by Drakulovic et al, randomized 39 mechanically ventilated patients to the semi recumbent position and 47 to the supine position (30). They found that patients in the semi recumbent group were significantly less likely to develop microbiologically confirmed pneumonia ($p=0.018$). Kinetic beds turn the patient slowly and continuously along the longitudinal axis, thereby promoting drainage of airway secretions. Several studies have shown a decrease in the development of VAP with their use (31, 32, 33, 34). Their increased cost, however, has prevented them from widespread use and acceptance.

There has been some concern that the condensate which accumulates in the ventilator circuit tubing may act as a reservoir for the development of microorganisms, which if aspirated, may lead to VAP. The routine changing of these circuits has therefore been studied in the prevention of VAP. Several randomized controlled trials have failed to show a decrease in the development of VAP with scheduled circuit changes (35, 36, 37) and routine changes of these circuits is not recommended.

Conventional suctioning of the airway may be performed via open or closed systems. It has been postulated that the use of closed systems may decrease the potential for contamination of the airway and thus decrease the rate of VAP. Several studies, however, have failed to show a difference in prevention of VAP between the two methods (38, 39, 40).

The use of humidifiers, early tracheostomy and weaning protocols are all still under investigation to potentially prevent development of VAP.

Gastrointestinal Management

In the normal healthy adult bacteria would not survive the acidic environment of the stomach. When the pH is increased to a level > 4, as may occur in patients receiving antacids, H2 blockers, or alkalinized enteral feeds, bacteria may multiply and overgrowth leads to colonization with potentially pathogenic organisms. Some studies have suggested that colonization of the stomach precedes colonization of the upper airways and subsequent VAP (41). This finding, however, has not been confirmed (42, 43).

Patients receiving mechanical ventilation are at increased risk for the development of stress ulcers and typically receive prophylaxis against them. Prophylaxis with antacids or H2 blockers, which neutralize gastric contents, has been implicated in the development of VAP. In contrast, sucralfate acts to form a protective coating along the lining of the stomach but does not neutralize gastric secretions and therefore has been studied as an alternative to antacids and H2 blockers to reduce the development of VAP. A randomized controlled trial comparing antacids, ranitidine and sulcralfate found that patients who received sucralfate had significantly fewer episodes of late-onset VAP (44). Several other studies have confirmed lower rates of pneumonia with the use of sucralfate and a meta-analysis of existing studies found a significant decrease in the incidence of VAP in these patients versus those receiving antacids or H2 blockers (8). Some authors believe sucralfate itself may have some antibiotic properties. When compared to placebo, however, sucralfate has not been shown to prevent VAP (45, 46). In the largest randomized controlled trial to date by Cook et al, 1200 patients requiring mechanical ventilation were randomized to receive sucralfate, ranitidine or placebo for stress ulcer prophylaxis (47). Patients in the sucralfate group had significantly higher events of clinically important gastrointestinal bleeding. In addition, there was no difference between the two groups in mortality or length of stay in the ICU. Given these results the potential risk of gastrointestinal bleeding needs to be weighed against the risk for VAP before an agent for prophylaxis is chosen.

The presence of a nasogastric tube is an independent risk factor for the development of VAP (8). The nasogastric tube likely increases the risk for VAP by increasing colonization of the oropharynx and increasing reflux which may lead to aspiration. It has been postulated that placing a jejunal tube, instead of a gastric tube, may decreased reflux and therefore decrease the risk of VAP. Studies comparing these, however, have not shown a difference in the rate of pneumonia between the two groups (48). In addition to the risk associated with the tube, enteral feeds are alkaline and neutralize the gastric contents, which may support the growth of potentially virulent bacteria. Acidification of tube feeds has been evaluated in the prevention of VAP, but has not been shown to be effective (49). The use of enteral versus parenteral nutrition has also been compared, but again no difference has been found between the two groups (50).

Selective decontamination of the digestive tract (SDD) refers to the use of topical and or intravenous antibiotics to "sterilize" the gut, decreasing colonization with potential pathogenic organisms and thereby reducing the rate of VAP. The current studies are difficult to interpret due to differences in study design and patient population. While some studies have shown a potential benefit, a clear decrease in mortality has not been demonstrated. In addition, there is real concern for the development of bacterial resistance and superinfection with the use of SDD and as such this is not a recommended form of prevention (19).

Table 2. Summarized Strategies for the Prevention of VAP

Strategy	Grade*
Effective Strategies	
Hand washing	B
Gown/Gloves**	B
Non-nasal intubation	D
Subglottic secretion drainage	A
Kinetic beds	B
Semi recumbent position	B
Non-invasive positive pressure ventilation	A
Adequate cuff inflation pressure (>25 cm H2O)	C
Avoidance of unnecessary re-intubation	C
Stress ulcer prophylaxis sucralfate vs. H2 blockers	B
Topical plus IV antibiotics***	(Meta-Analysis)
Ineffective Strategies	
Scheduled changes of ventilator circuit	A
Use of closed versus open suctioning systems	B
Chlorhexidate oral rinses	B
Motility Agents	B

* Grade A: supported by at least 2 randomized controlled investigations; B: supported by at least one randomized, controlled investigation; C: supported by nonrandomized, concurrent-cohort or historical cohort investigations or case series; D: supported by randomized, controlled investigations of other infections.
** For selected patients with resistant pathogens
*** The use of topical plus IV antibiotics is not recommended secondary to concern for development of antibiotic resistance.

Diagnosis

The lack of standardized diagnostic criteria for ventilator associated pneumonia remains a dilemma that affects all areas of research. Without a gold standard, it is difficult to compare and interpret data on epidemiology, diagnosis or management. Previously, histologically proven pneumonia, either by lung biopsy or autopsy, has been considered a reliable method for comparison. However, the diagnostic accuracy of this technique has recently been called into question (51). Some studies have reported inter-observer differences between the pathologists who review these specimens.

Clinical criteria for the diagnosis of VAP typically include radiographic evidence of new or progressive infiltrate, plus two or more of the following:

- Fever,
- leukocytosis, or
- purulent tracheal secretions

The diagnosis of VAP by clinical criteria alone, however, is not a reliable method. Autopsy studies have shown the clinical prediction of pneumonia is neither sensitive (54-72%), nor specific (57-83%) (8). A post mortem study by Torres et al was done to evaluate the usefulness of clinical criteria in the diagnosis of pneumonia (52). Patients were considered to have clinical pneumonia if they had new and persistent infiltrate on chest radiograph plus two or more of the following: 1) fever, with temperature > 38.3 * C; 2) leukocytosis, with WBC > 12 x 10(9)/ml or; 3) purulent tracheal secretions. As defined, the clinical prediction of VAP was only 69% sensitive and 75% specific. Each clinical predictor was separately evaluated and they found fever to have a sensitivity of 55% and specificity of 58%, purulent secretions 83% and 33%, and radiographic infiltrate 78% and 42%, respectively.

Radiograph of the chest is most helpful when it is normal and used to rule out pneumonia. Infiltrates seen on plain chest film, however, are not specific. Wunderink et al performed an autopsy study to evaluate the use of different radiographic signs in the diagnosis of VAP. They studied air bronchograms, alveolar infiltrates, the silhouette sign, cavitary lesions, fissure abutment, atelectesis, and asymmetric infiltrates superimposed on diffuse bilateral infiltrates. The study showed, by step wise logistic regression, that only air bronchograms correlated with pneumonia, correctly predicting pneumonia 64% of the time (53). In patients with ARDS, no radiographic sign correlated with autopsy proven pneumonia.

Non-Bronchospcopic techniques

The use of routine, qualitative cultures by endotracheal aspirate (ETA) is frequently inconclusive and generally not recommended. Qualitative cultures may have a high sensitivity (57-88%), but are not specific (specificity 0-33%) (54). The high number of false positives reflects tracheal colonization with organisms that may not represent a true pathogen. When qualitative cultures are used to make clinical decisions a large number of patients may receive unnecessary antibiotic therapy.

Jourdain et al evaluated the usefulness of quantitative cultures of ETA in the diagnosis of VAP (55). They found the cut off of 10^{6} CFU/ml to have the greatest diagnostic accuracy with a sensitivity of 68% and a specificity of 84%. An ETA with greater than 10 epithelial cells per low power field suggests oropharyngeal contamination and should be considered unreliable. A study by Morris reported that 85% of tracheal aspirates should be rejected based on this criteria (56). Two studies have compared outcomes in patients with VAP who were diagnosed by either non-invasive (ETA) or invasive techniques (bronchoalveolar lavage [BAL] or protected specimen brush [PSB]), (13, 14). Although, one study found an increase frequency of antibiotic changes in the invasive group, neither study demonstrated a difference in mortality or ICU days between the two groups.

Non-bronchoscopic techniques, such as mini-BAL and blind PSB, sample distal secretions blindly using a catheter that is wedged in the bronchial tree. These techniques have many advantages over bronchoscopy. They are less invasive, associated with a decreased cost and are better tolerated by the patient than BAL or PSB. Perhaps the greatest advantage is that they are easy to use, in fact these techniques can be performed by respiratory technicians. Post mortem studies have found mini BAL and blind PSB to have an acceptable diagnostic accuracy, with sensitivity and specificity of mini BAL of 78% and 86% and of blind PSB of 78% and 100%, respectively (8). A study by Papazian et al compared blind techniques to invasive bronchoscopy and showed both techniques to have a similar accuracy, in fact blind PSB was found to be more sensitive than PSB using fiber optic bronchoscopy (82% versus 42%, $p = 0.05$) (57).

Bronchoscopic techniques

Brochoalveolar lavage is used to sample a large segment of alveoli. It involves wedging a bronchoscope into a segmental bronchus, then introducing and aspirating saline aliquots which are collected and sent to the lab for analysis. Since the bronchoscope must first pass through the endotracheal tube and upper airways before reaching the bronchus there is a risk of contamination. Protective specimen brush uses a telescoping double lumen catheter which passes through the upper airways in an attempt to avoid contamination. When the segmental bronchus is reached the outer catheter is retracted revealing a brush which can then sample the area. Specimens from both techniques should be sent for gram staining, which may help guide early therapy, and all bacterial growth should be quantitated. BAL has an accepted diagnostic threshold of 10^{4} to 10^{5} CFU/ml, while the diagnostic threshold for PSB is 10^{3} CFU/ml. Bronchoalveolar lavage specimens with > 1% epithelial cells should be considered contaminated. By pooling data from 18 different studies, Chastre et al found PSB to have a sensitivity of 89% and a specificity of 94% (8). In the same review, 23 studies evaluating the diagnostic accuracy of BAL were pooled and found BAL to be 73% sensitive and 83% specific. Studies directly comparing BAL and PSB have not found a significant difference between the two techniques (58).

Patients whose initial antibiotic regimen was later found to be inappropriate have a higher mortality rate than patients treated with adequate antibiotics. This fact has been confirmed by several studies (11, 12, 13, 14). Many authors believe that invasive bronchoscopy may be used to guide initial therapy, and subsequently decrease mortality. Studies involving outcomes, however, have failed to show a clear mortality benefit of invasive bronchoscopy over non-invasive techniques.

Sanchez-Nieto et al performed a prospective randomized clinical trial to evaluate outcomes after invasive versus non-invasive diagnosis of VAP (59). They included 51 mechanically ventilated patients who were randomized to either invasive diagnosis with PSB, BAL and ETA (n=24) or non-invasive diagnosis with ETA only (n=27). The invasive group underwent more changes in antibiotics than the non-invasive group ($p< 0.05$). However, there was no difference in mortality, duration of mechanical ventilation or length of ICU stay between the two groups.

A prospective observational study performed by Luna et al evaluated 132 patients who were mechanically ventilated and met clinical criteria for VAP (12). 65 patients had VAP as defined by bacterial growth of $> 10^4$ CFU/ml on BAL, while 67 patients did not meet BAL criteria for VAP. Patients who had BAL criteria for the diagnosis of VAP had no difference in mortality when compared with patients who did not have VAP. Patients whose initial antibiotic regimen was later deemed to be inappropriate by bronchoscopy evaluation had a significant increase in mortality ($p < 0.001$). After bronchoscopy 42 patients had their antibiotic regimen changed to cover organisms found on examination, however, the mortality in this group remained the same as those who continued to receive inadequate therapy.

A study by Fagon et al did show improved survival in patients who underwent invasive diagnosis of VAP at day 14, however, this change in survival was no longer significant at day 28 (60). Many critics believe that the methods of analysis used magnified results which may not be clinically relevant. In the end mortality is not changed with the use of invasive techniques.

If there is no clear mortality benefit to invasive techniques why use fiber optic bronchoscopy at all? As previously stated, the use of clinical criteria for the diagnosis of VAP may lead to over-diagnoses and excessive antibiotic usage. The use of invasive techniques has been associated with a decrease in the total number of antibiotics used. This reduction in antibiotic usage decreases selection pressure and theoretically may lead to a decrease in multi-resistant organisms and super-infection. In addition targeted use of antibiotics may reduce cost and toxicity related to these drugs.

A prospective cohort by Heyland et al examined 141 mechanically ventilated patients with a clinical suspicion of VAP (61). Ninety-two patients underwent bronchoscopy and 49 patients did not. Through a physician survey they found the use of bronchoscopy was associated with improved confidence in their diagnosis ($p = 0.03$) and increased comfort level with their management plan ($p = 0.02$). As a result, patients who underwent invasive diagnosis received fewer antibiotics overall ($p = 0.05$) and were more likely to have all of their antibiotics discontinued ($p = 0.04$). Other studies have shown a similar decrease in total number of antibiotics received in patients who underwent bronchoscopy (60, 62).

Many infectious and non-infectious conditions may mimic VAP clinically. If clinical criteria alone is used the true source of the patients symptoms may never be found. The use of fiber optic bronchoscopy, which fails to identify pneumonia, may alert the clinical team to search for other sources of the patients' symptoms. Many authors believe this may be the most important benefit of bronchoscopy (8).

At present there is no uniformly accepted diagnostic standard for VAP. More outcome based studies are needed to compare non-invasive diagnostic techniques (ETA, mini-BAL and blind PSB) with invasive bronchoscopy (with BAL or PSB). Because of the mortality benefit of early appropriate therapy, any diagnostic technique employed should not delay the start of antibiotics.

Treatment

Empiric Treatment

Research on the most appropriate empiric therapy for VAP is lacking. The last guidelines published by the American Thoracic Society on the treatment of hospital acquired pneumonia (which includes VAP) were released in 1996 (Table 3, 4, 5) (63). These guidelines are frequently quoted in the literature, however, rigorous evidence to support them is missing.

Most experts agree that the choice of therapy should be individualized to institution and patient. Treatment should be guided by hospital epidemiologic data if possible. The CDC recommends the use of routine surveillance cultures of patients in the ICU (20). In addition to adding data to hospital wide epidemiology, these cultures may identify potential pathogens in individual patients. In addition, certain patient characteristics may help guide empiric therapy choices. Patients who develop early onset VAP typically are infected with the same bacteria responsible for most community acquired pneumonias and may be easier to treat. While patients who develop late onset VAP are at risk for polymicrobial infections with more virulent and often resistant pathogens (such as *Pseudomonas aeruginosa*, *Acinetobacter baumanii*, and Methacillin-Resistant *Staphylococcus aureus*). Whenever possible early gram stain results should be used to guide treatment choices, however, if these are not readily available they should not delay therapy.

Table 3. Mild to Moderate HAP without Risk Factors.

Likely Organisms	Empiric Therapy
Enteric GNB	Second Generation Cephalosporin
	OR
MSSA*	Beta-lactam/Beta-lactamase PCN**
	OR
Streptococcus pneumoniae	Floroquinolone

* MSSA = Methicillin-Sensitive *Staphylococcus Aureus*
** PCN = Penicillin

Table 4. Mild to Moderate HAP with Risk Factors.

Risk Factors	Likely Organism	Empiric Therapy
Recent Abdominal Surgery Witnessed Aspiration	Anaerobes	Clindamycin
Coma Head Trauma DM Renal Failure	*Staphylococcus Aureus*	Vancomycin
Prolonged ICU stay Steroids Prior antibiotics Structural lung disease	*Pseudomonas Aeruginosa*	Same as Severe HAP

Table 5. Severe HAP

Definition of Severe HAP

- ICU admission
- Need for MV of > 35% oxygen to maintain oxygen saturation > 90%
- Rapid progression of infiltrate on radiograph
- Evidence of sepsis with hypotension or organ dysfunction

Likely Organisms

Psuedomonas aeruginosa
Acinetobacter baumanii
Methicillin-Resistant *Staphylococcus aureus*

Empiric Therapy

Aminoglycoside OR Ciprofloxacin
\+
Anti-pseudomonal penicillin OR Imipenim OR Aztreonam
+/-
Vancomycin

Mono-therapy versus Combination Therapy

Traditionally empiric therapy for VAP involves the use of one or two broad spectrum agents which cover both gram-negative and gram-positive bacteria. Some researchers worry that the use of a single agent, especially for late onset VAP, may not be adequate. Trouillet et al showed that more than 45% of patients with late onset VAP and prior antibiotic exposure had inadequate therapy with any single agent (19). With the knowledge that adequate initial therapy improves survival, these researchers have suggested the use of combination therapy until culture results are available. Evidence to support the use of combination therapy over mono-therapy, however, is lacking. Several studies have shown mono-therapy to be at least equivalent to combination therapy.

A prospective randomized trial by Cometta et al compared imipenem alone with imipenem plus netilmicin for the empiric treatment of nosocomial pneumonia (64). One hundred and fifteen patients with VAP were enrolled. The use of mono-therapy with imipenem was found to be as effective as the use of combination therapy. Both groups had similar rates of resistance and superinfections. There was, however, an increased rate of nephrotoxicity in patients who received an aminoglycoside.

More studies need to be done to compare the use of mono-therapy versus combination therapy for the empiric treatment of VAP.

Rotation of Antibiotics

There is early evidence that scheduled rotations of prescribed antibiotics are associated with a decrease in resistant organisms. Kollef et al evaluated the impact of scheduled antibiotic rotation for empiric therapy on the incidence of VAP (65). For a 6 month "before period" a third generation cephalosporin was used for the empiric therapy of VAP. For the 6 month "after period" empiric therapy was changed to a floroquinolone. They found a decreased incidence of VAP in the after period (6.1 vs. 11.6, $p = 0.028$). This decreased incidence was attributed to a decrease in antibiotic resistant gram negative bacilli (0.9 versus 4%, $p = 0.013$). Despite these results, the scheduled rotation of antibiotics remains controversial and questions remain about the long term impact this practice may have on resistance patterns and outcome.

Length of treatment

There is no consensus on length of treatment for VAP. Most experts agree that a 14 day course is sufficient to treat VAP, however, for certain organisms, such as *Pseudomonas aeruginosa* and *Acinetobacter baumannii*, a longer course (21 days) may be necessary. There is some concern, however, that a prolonged course may lead to increased cost, toxicity or selection of resistant organisms. These concerns have lead researchers to test a shorter duration of treatment.

A recent prospective randomized double blinded trial by Chastre et al compared 8 versus 15 days of antibiotic therapy for VAP (66). Four hundred and one patients with bronchoscopy proven VAP who were deemed to have appropriate antibiotic therapy were enrolled. One hundred and ninety-seven patients were assigned to the 8 day treatment group and 204 patients to the 15 day treatment group. Patients who received the shorter course of therapy had no difference in mortality or recurrence of pulmonary infections than those who received the longer course. Those patients in the 8 day group, however, did have significantly more antibiotic free days. Of note, patients whose VAP was caused by non-fermenting gram negative bacilli (GNB) did have a higher incidence of pulmonary recurrence (but no increase in mortality). Recurrence in this circumstance was more likely to be secondary to a resistant pathogen. As a result of this study, it seems that a select group of patients may benefit from a shorter course of therapy. However, it is still generally recommended to treat VAP due to non-fermenting GNB for 14-21 days.

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